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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,939	11/25/2003	Richard B. Roth	SEQ-4071-UT	9634

47328 7590 08/23/2006

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EXAMINER	
SITTON, JEHANNE SOUAYA	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/722,939	ROTH ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,15-17,48-52,56 and 57* is/are pending in the application.

4a) Of the above claim(s) *51 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,15-17,48-50,56 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/05, 7/06*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, and a polymorphism at position 39977 in SEQ ID NO: 1, in the reply filed on 6/19/2006 is acknowledged. The traversal is on the ground(s) that a) claims 51 and 52 should be included in Group 1 as there is no undue search burden because search for claims 1 and 48 will pertain to the search for subject matter of claims 51 and 52 and b) that the election of the polymorphisms should not be a requirement for restriction but instead a species election. These arguments have been thoroughly reviewed but were not found persuasive. Searching the art for breast cancer preventative procedures such as selective hormone receptor modulators will not provide art relating to breast cancer detection procedures such as biopsy procedure. These are entirely different procedures which require different steps and are not obvious over each other. The methods steps of claim 48 require administering one or the other. Accordingly, the method of detection and the method of prevention are patentably distinct and constitute a search burden. Claims are required to be searched not only for art purposes for patentability under 35 USC 102 and 103, but also under 35 USC 112, first paragraph. The search for breast cancer preventative procedure in claim 48 as well as the myriad of breast cancer preventative procedures listed in claims 51 and 52 represent a serious search burden on the office. With regard to the restriction between the polymorphisms as recited in claim 1, it is noted that claim 1, directed to SEQ ID NO: 1, is linking with regard to the polymorphisms listed in claims 3 and 4, for example. The restriction requirement and how it affects the examination of claim 1, for example, is set forth below.

Claims 1, 2, 16, 17, 48 in part directed to detection, and 56 link(s) the polymorphisms in claims 3-5, 15, and 49. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s), claims 1, 2, 16, 17, 48 directed to detection, and 56. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104. Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312. Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. In re Ziegler, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The traversal that the restriction requirement between polymorphisms should be an election of species has been thoroughly reviewed but was not found persuasive as the nucleic acid molecules comprising each polymorphism are structurally and functionally distinct. A search for each polymorphism is not coextensive. Searching must be conducted not only in sequence databases such as Genbank, but in the patent and non patent literature as well as polymorphism databases such as dbSNP because sequence databases, such as Genbank, do not

normally provide information on SNPs. The position of each SNP in the chromosome does not decrease the search burden as polymorphisms are not usually referenced in journal articles with regard to the position on the chromosome. A complete search for each polymorphism is not coextensive. Search and examination of more than one of the polymorphisms for patentability presents a serious burden on the office. The response's assertion that the claimed polymorphisms are all associated with breast cancer is not found persuasive. As can be seen in table 10, the majority of the claimed polymorphisms are not significantly associated with breast cancer ($p > .05$).

The requirement is still deemed proper and is therefore made FINAL.

Compact Disc Submission

2. Portions of this application are contained on compact disc(s). When portions of an application are contained on a compact disc, the paper portion of the specification must identify the compact disc(s) and list the files including name, file size, and creation date on each of the compact discs. See 37 CFR 1.52(e). Compact disc labeled "CRF" is not identified in the paper portion of the specification with a listing of all of the files contained on the disc. Applicant is required to amend the specification to identify each disc and the files contained on each disc including the file name, file size, and file creation date.

3. This application contains compact disc(s) as part of the originally filed subject matter, but does not contain an incorporation by reference statement for the compact discs. See 37 CFR 1.77(b)(4). Applicant(s) are required to insert in the specification an incorporation-by-reference of the material on the compact disc(s).

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 15-17, 48-50 and 56-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to identifying any subject at risk of breast cancer or detecting breast cancer, or selecting any subject that will respond to a treatment of breast cancer which comprises detecting the presence or absence of one or more polymorphic variations in a) SEQ ID NO: 1, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 1, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 1, or d) any fragment of a, b, or c; whereby the presence of the polymorphism is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or

more polymorphisms, or selecting a subject that will respond to the breast cancer treatment based upon the presence or absence of the one or more polymorphic variations. The claims are also broadly drawn to detecting one or more polymorphic variations in linkage disequilibrium with the polymorphism at position 39977 of SEQ ID NO:1.

The genus encompassed by the claims is a broad variable genus as discussed below. The claims encompass not only detection of any polymorphism in SEQ ID NO: 1, but in sequences which encode a polypeptide encoded by SEQ ID NO: 1, sequences which encode a polypeptide with 90% identity to a polypeptide encoded by SEQ ID NO: 1, as well as sequences comprising fragments of such. The claims therefore encompass detection of polymorphisms in a large genus of variants, mutants and homologs of SEQ ID NO: 1, from any source. However, the specification does not teach degenerate variants of SEQ ID NO:1, nor does the specification teach any homologs of SEQ ID NO: 1 which encode a polypeptide with 90% identity with a polypeptide encoded by SEQ ID NO: 1. The specification does not teach any polymorphisms whatsoever, in any variants, mutants or homologs encompassed by sections b-d of claims 1, 48 and 56, or any polymorphisms in any other species, let alone any SNPs that are statistically associated with breast cancer. The claims also broadly encompass identifying SNPs in any subject, which encompasses any species, however the specification only teaches the identification of 4 particular statistically associated polymorphisms in SEQ ID NO: 1 in humans.

The broad genus further encompasses detecting polymorphic variations that are in linkage disequilibrium with the elected polymorphic variation at position 39977 of SEQ ID NO: 1. However, the specification does not teach any particular SNPs which are in linkage disequilibrium with the elected SNP. It is clear from table 10, that a SNP, by virtue of being in

the DLG1 "region" is not necessarily associated with breast cancer. The specification provides no predictable correlation between any particular SNP in linkage disequilibrium with the elected SNP.

The broad genus also encompasses (claims 56 and 57) selecting a subject that will respond to treatment of breast cancer based on the presence or absence of any SNP in the broadly claimed regions noted above, as well as the elected SNP. However the specification provides no teaching or guidance whatsoever as to whether any of the identified SNPs, including the T variation at position 39977 of SEQ ID NO:1 are predictive of a subject's response to treatment. It is not known if the T at position 39977 of SEQ ID NO: 1 is indicative of a subject responding or not responding to treatment or whether the variant is indicative of response to certain types of treatment, for example a particular chemotherapeutic drug, but not others. The specification provides absolutely no guidance as to whether any of the disclosed SNPs or broadly encompassed SNPs affect the function of the gene in any way to predict a subject's response to treatment.

The current claims encompass detection in a large variable genus of nucleic acids which comprise polymorphisms in any region of the DLG1 gene or homolog from any source. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided in the specification. However, the specification only teaches of 4 particular polymorphisms for which data is provided (eg: T/C at position 39977 of SEQ ID NO: 1). With regard to the elected position, the specification teaches that a T at position 39977 of SEQ ID NO: 1 was statistically associated (p=0.0009) with breast cancer (table 6B). Thus, applicant has express possession of only 4 particular polymorphisms in SEQ ID NO: 1 which are

associated with breast cancer, in a genus which comprises hundreds of millions of different possibilities.

The broad variable genus is not represented by the particularly 4 named variants in table 6B of the specification for the reasons which follow. In the broadly claimed invention, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with breast cancer or therapeutic response is provided. However, no predictable correlation between the structural alterations of the 4 polymorphisms disclosed and breast cancer is provided by the specification. The specification does not teach the function of polymorphisms of DLG1 nor how their function, or lack of function, or altered function are predictably associated with breast cancer or therapeutic response. The specification teaches 21 SNPs (table 10) were found in SEQ ID NO: 1, but that only 4 particular polymorphisms exhibited a statistically significant association with breast cancer. Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of breast cancer association or treatment. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 39977 of SEQ ID NO: 1), but only teaches 2 out of 4 possible variations at each position (T to C at position 39977). The specification does not teach if a G or an A would be statistically associated with breast cancer or treatment nor does it provide any guidance as to whether the particular nucleotide variant even exists. The specification provides no guidance that any alteration, in any DLG1 gene, in any subject, is diagnostic for increased risk for breast cancer or predictive of therapeutic response. With regard

to claims 56 and 57, the specification provides no teaching or guidance as to whether any SNP in the broadly encompassed sequences has any predictable response to therapy.

Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. No written description of alleles, of upstream or downstream regions containing additional sequence, which are associated with any phenotype are described in the specification. Additionally, the specification provides no evidence that any SNP at such position, in either humans, or mice or dogs for example, provides a predictable association with breast cancer or predictive of therapeutic response. The polymorphisms shown are not representative of the genus of any polymorphism associated with breast cancer because it is not clear which polymorphisms within a DLG1 region would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the breast cancer may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification provides no guidance that the specific alleles exist in other species, therefore, there is no teaching or guidance as to the identity of alleles in linkage disequilibrium with recited alleles in other species. The specification fails to provide any teaching or guidance as to what the structure of phenotypically associated alleles would be in variants or homologs of SEQ ID NO: 1 in humans, or in DLG1 or variants or homologs in other species. Accordingly, the 4 particularly disclosed variants are not representative of the large variable genus encompassed by the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. The skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention. However, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

7. Claims 1-5, 15-17, 48-50 and 56-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying a human subject at risk of breast cancer comprising a) detecting the presence of a T at nucleotide position 39977 of SEQ ID NO: 1 and b) identifying the human subject as having an increased risk of breast cancer or administering a breast cancer detection procedure, does not reasonably provide enablement for identifying a subject at risk of breast cancer or detecting breast cancer, or selecting a subject that will respond to a treatment of breast cancer which comprises detecting the presence or absence of one or more polymorphic variations in a) SEQ ID NO: 1, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 1, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 1, or d) any fragment of a, b, or c; whereby the presence of the polymorphism is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms, or selecting a subject that will respond to the breast cancer treatment based upon the presence or absence of the one or more polymorphic variations. The claims are also limited to detecting one or more polymorphic variations in linkage disequilibrium with the polymorphism at position 39977 of SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are broadly drawn to identifying any subject at risk of breast cancer or detecting breast cancer, or selecting any subject that will respond to a treatment of breast cancer which comprises detecting the presence or absence of one or more polymorphic variations in a) SEQ ID NO: 1, b) a nucleotide sequence which encodes a polypeptide encoded by SEQ ID NO: 1, c) a nucleotide sequence which encodes a polypeptide that is 90% or more identical to the amino acid sequence encoded by SEQ ID NO: 1, or d) any fragment of a, b, or c; whereby the presence of the polymorphism is indicative of the subject being at risk of breast cancer, or administering a breast cancer detection procedure based on the presence or absence of the one or more polymorphisms, or selecting a subject that will respond to the breast cancer treatment based upon the presence or absence of the one or more polymorphic variations. The claims are also broadly drawn to detecting one or more polymorphic variations in linkage disequilibrium with the polymorphism at position 39977 of SEQ ID NO:1.

The nature of the claimed invention, therefore, requires the knowledge of predictive associations between any polymorphism in any of the recited nucleic acids, or any polymorphism in linkage disequilibrium with such, in any subject and a risk for breast cancer or therapeutic response to breast cancer treatment.

The amount of direction or guidance and presence/absence of working examples:

The specification teaches that SEQ ID NO: 1 is the genomic nucleotide sequence for the human DLG1 "region" (page 3). However, the specification does not teach which portions of SEQ ID NO: 1 are directed to the human DLG1 gene, where the regulatory regions, such as the promoter, lie, and whether the sequence comprises the entire gene. The specification teaches that a number of polymorphisms were identified in the sequence and teaches that a T variation at position 39977 of SEQ ID NO: 1 is statistically associated with breast cancer ($p=0.0009$; see page 74, table 6B). The specification teaches that a number of SNPs were identified in females with breast cancer (cases) and females without cancer (controls) and that SNPs were considered as being associated with breast cancer if the allele frequency between cases and controls was statistically significant (page 70, para 0232). The specification teaches 21 SNPs in the "DLG1 proximal region" were found (page 78, table 10), but only 4 are statistically associated with breast cancer.

However, the claims broadly encompass detection in variants, mutants and homologs of SEQ ID NO: 1 (sections b-d of claim 1, for example), and the specification does not teach whether any SNPs are statistically associated with breast cancer in such sequences. The claims are drawn not only to detection of any polymorphism in SEQ ID NO: 1, but in sequences which encode a polypeptide encoded by SEQ ID NO: 1, sequences which encode a polypeptide with 90% identity to a polypeptide encoded by SEQ ID NO: 1, as well as sequences comprising fragments of such. The claims therefore encompass detection of polymorphisms in a large genus of variants, mutants and homologs of SEQ ID NO: 1, from any source. However, the specification does not teach degenerate variants of SEQ ID NO:1, nor does the specification

teach any homologs of SEQ ID NO: 1 which encode a polypeptide with 90% identity with a polypeptide encoded by SEQ ID NO: 1. The specification does not teach any polymorphisms whatsoever, in any of the sequences encompassed by sections b-d of claims 1, 48 and 56, or any polymorphisms in any other species. The claims also broadly encompass identifying SNPs in any subject, which encompasses any species, however the specification only teaches the identification of 4 particular statistically associated polymorphisms in SEQ ID NO: 1 in humans.

The claims also encompass detecting polymorphic variations that are in linkage disequilibrium with the elected polymorphic variation at position 39977 of SEQ ID NO: 1. However, the specification does not teach any particular SNPs which are in linkage disequilibrium with the elected SNP. It is clear from table 10, that a SNP, by virtue of being in the DLG1 "region" is not necessarily associated with breast cancer. The specification provides no predictable correlation between any particular SNP in linkage disequilibrium with the elected SNP.

Further, claims 56 and 57 are specifically drawn to selecting a subject that will respond to treatment of breast cancer based on the presence or absence of any SNP in the broadly claimed regions noted above, as well as the elected SNP. However the specification provides no teaching or guidance whatsoever as to whether any of the identified SNPs, including the T variation at position 39977 of SEQ ID NO:1 are predictive of a subject's response to treatment. It is not known if the T at position 39977 of SEQ ID NO: 1 is indicative of a subject responding or not responding to treatment or whether the variant is indicative of response to certain types of treatment, for example a particular chemotherapeutic drug, but not others. The specification provides absolutely no guidance as to whether any of the disclosed SNPs or broadly

encompassed SNPs affect the function of the gene in any way to predict a subject's response to treatment.

The specification provides no universal correlation that any SNP in any of the claimed nucleic acids would be associated with breast cancer or response to treatment nor does it provide any way to predict which sequences within the broadly claimed sequences would be "breast cancer associated". Of 21 disclosed SNPs, the specification teaches a statistically significant association between only 4 SNPs and breast cancer, and does not teach any SNP which is predictive of response to treatment. Thus it is clear that "any" polymorphism in the encompassed nucleic acids would not be predictable of breast cancer association or treatment. It is further noted that the claims broadly encompass "any" polymorphic variation at the disclosed position (eg, elected position 39977 of SEQ ID NO: 1), but only teaches 2 out of 4 possible variations at each position (T to C at position 39977). The specification does not teach if a G or an A would be statistically associated with breast cancer or treatment nor does it provide any guidance as to whether these particular nucleotide variants even exist.

Additionally, the specification provides no guidance as to how the SNP at 39977 (T), or any of the other 3 statistically associated variants, function to provide for increased risk of breast cancer. The specification provides no structure/function correlation between the disclosed SNPs and breast cancer for the ordinary artisan to be able to predict which other positions within the claimed sequences might be predictably associated with the claimed phenotypes. While the elected T/C variant is taught to change the amino acid (R278Q) in the encoded protein, the specification does not teach if the function of the encoded protein is altered. It is not clear if any

other variant at that position would encode the same or different amino acid change or whether any other amino acid change at position 278 would have the same effect.

It is not known whether this polymorphism exists in other variants or homologs or other mammalian genes or what other variation positions would be in another gene or whether a polymorphism would have the same effect in another gene, or what the identity of that polymorphism might be. Therefore, the skilled artisan would be unable to predictably correlate any other structural change in any other region of DLG1 in any other species. The elected allele could be part of a breast cancer-associated haplotype, however the causative mutation is not necessarily one of the SNPs taught in the specification. The causative mutation could be in a gene thousands of nucleotides away, however the specification provides no indication of what this allele might be.

The specification provides no predictable association that any alteration, in any DLG1 gene, in any subject, is diagnostic for increased risk of breast cancer or therapeutic response. No common element or attributes of the sequences are disclosed which would permit selection of sequence polymorphisms as diagnostic for an increased risk of breast cancer or predictive of therapeutic response. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with breast cancer or therapeutic response is provided. Further, these claims expressly encompass allelic variants including insertions, deletions, substitutions and transversions at thousands of different sites. However, the specification provides no evidence that any polymorphic variation at such positions, in either humans, or mice or dogs for example, provides a predictable association with breast cancer or therapeutic response. The

polymorphisms shown are not predictive of the genus of any polymorphism associated with breast cancer because it is not clear which polymorphisms within "any" DLG1 sequence would have the same affect. It is not clear whether the polymorphisms shown are causative for the detected phenotype or whether they may simply represent markers for another gene that is in linkage disequilibrium with the specific alleles at issue, and the actual gene which is involved in the detected breast cancer association may be tens of thousands of nucleotides distant from the polymorphisms described in the specification. The specification does not teach the function of polymorphisms of SEQ ID NO: 1, nor how their function, or lack of function, or altered function are predictably associated with breast cancer or therapeutic response.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the prior did not teach the function or biological activity of DLG1. The specification demonstrates the unpredictability of this invention since 17 out of 21 of the identified SNPs in SEQ ID NO: 1 were not statistically significant and are not breast cancer associated. Thisted et al (see galston.uchicago.edu/~thisted/, pages 1-5) notes that "It has become scientific convention to say that p-values exceeding .05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their effect (see page 5).

Further, there is a large body of knowledge in the prior art related to polymorphisms in general, and their association with diseases or disease states, as well as drug or therapeutic response. However, the art is highly unpredictable with regard to the functionality of polymorphic sites in genomic DNA. After a screening assay identifies polymorphisms, it is

unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state, a physiological state, or drug metabolism or response. For example, Hacker et al. teaches that they were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the p-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 1998; 281 (5384):1787-1789). Further, in some cases where multiple polymorphisms were identified in a gene, some of these were demonstrated to be disease associated and some were not. For example, Blumenfeld et al. (WO 99/52942) disclose a number of polymorphisms in the FLAP gene. While Blumenfeld et al. were able to demonstrate that some of these polymorphisms are associated with patients having asthma Blumenfeld et al found that some of these polymorphisms are not (see Figure 3). For example, the marker 10-35/390 was demonstrated to be associated with asthma, with a p value of 0.00229, while the marker 10-33/327 was determined not to have a statistical association with asthma ($p=0.294$). The unpredictability of the functionality or use of SNPs is not limited to diagnostic uses, but is found in therapeutic response as well. Malhotra et al (Am. J. Of Psychiatry, vol. 161, pages 780-796, May 2004) teaches that while a T102C polymorphisms in the serotonin 5-HT2A gene was reported to have a significant association with the failure to respond to clozapine in 149 patients with chronic schizophrenia, such effect was not able to be

replicated in a series of subsequent studies (see page 7829 col 2). Malhotra et al teach that definitive studies in larger group sizes, prospective clinical data, and comprehensive analysis of the gene will be needed to further address the role of this gene in antipsychotic drug response (see page 783, col. 1).

In the instant case, the specification only provides information that the T/C variant exists in humans and is associated with breast cancer , but provides no guidance that it has any effect whatsoever on the expression or activity of human DLG1 or the broadly claimed sequences let alone any potential association with therapeutic effect.

The level of skill in the art:

The level of skill in the art is deemed to be high, however the experimentation required to practice the broadly claimed invention is even higher.

The quantity of experimentation necessary:

The quantity of experimentation in this area is extremely large as it requires analysis of each position in SEQ ID NO: 1, as well as the broadly encompassed mutants, variants, and homologs encompassed by claims 1, 48 and 56, to determine whether any alteration at each position is associated breast cancer or therapeutic response and to identify which variations are predictably associated with breast cancer in any subject. As neither the art nor the specification provide guidance as to which alterations at positions throughout DLG1 are predictably associated with breast cancer or therapeutic response, such analysis is replete with trial and error experimentation, with the outcome of each analysis being unpredictable. Screening each

possible alteration in the broadly claimed genomic sequences, including SEQ ID NO: 1, represents an inventive and unpredictable undertaking in itself, with each of the many intervening steps, not providing any guarantee of success.

In order to practice the invention as claimed, one would first have to establish that a predictive relationship exists between the disclosed polymorphisms and breast cancer or therapeutic response in any subject. Further, the scope of many of the claims requires knowledge of an association between all mutations in any DLG1 gene and breast cancer or therapeutic response in humans or any species. Due to the scope of the claims, one of skill in the art would be required to further undertake extensive trial and error experimentation with a large number of patients with breast cancer, as well as patients being different therapy, and controls, to determine mutations that share a predictive correlation with breast cancer or therapeutic response.

Thus, given the broad claims in an art whose nature is identified as unpredictable, the state of the prior art, the lack of guidance in the specification, the breadth of the claims and the quantity of experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention commensurate in scope with the claims.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton

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Art Unit 1634
8/21/06